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● FUNGICIDE FACTSHEET

CHLOROTHALONIL

The fungicide chlorothalonil (commonly sold under the trade names Daconil and Bravo) is typically used on peanuts, tomatoes, potatoes, lawns, turf, and roses. It is the second most widely used agricultural fungicide in the U.S.

Chlorothalonil is irritating to eyes and skin. People exposed to chlorothalonil can become sensitized to the fungicide and develop severe or persistent reactions.

In laboratory tests, chlorothalonil causes kidney damage, mild anemia, liver damage, embryo loss during pregnancy, oxidative DNA damage (damage to the cell's genetic material), and cancers of the kidney and forestomach. Most of these effects have been observed in several test species. It is classified as a "probable human carcinogen" by the U.S. Environmental Protection Agency.

Chlorothalonil residues are found regularly on celery and green beans. It has been found in groundwater in four states, in the air approximately a mile from chlorothalonil-treated fields, and in Bering Sea fog and seawater samples.

Chlorothalonil is very highly toxic to fish, and concentrations as low as 2 parts per billion can cause gill damage and anemia. It is also toxic to shrimp, frogs, beneficial microorganisms, and earthworms. In plants it causes a variety of effects, including reductions in yield.

Chlorothalonil is contaminated with the carcinogen hexachlorobenzene. Its major breakdown product is about thirty times more acutely toxic than chlorothalonil itself and is more persistent in soil.

BY CAROLINE COX

Chlorothalonil (see Figure 1) is a fungicide commonly sold under the trade names Daconil and Bravo. Its primary manufacturer in the U.S. is ISK Biosciences Corporation.[1]

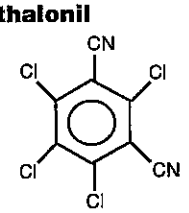
Use

Chlorothalonil has both agricultural and household uses. It is the second most widely used agricultural fungicide (in terms of pounds used per year) with applications totalling 11 million pounds annually. Only the fungicide sulfur is more widely used. Peanuts, tomatoes, potatoes, onions, and celery are frequently treated with chlorothalonil.[2] Georgia is the state with the highest agricultural use because of its large peanut acreage.[3] (See Figure 2.) Over 2.5 million applications are made annually in U.S. homes and yards. Lawns account for about a third of its use, and roses about a quarter.[4] (See Figure 3.)

Mode of Action

Chlorothalonil's mode of action involves its combination with a molecule called glutathione inside fungus cells. As these glutathione-chlorothalonil derivatives form, they tie up all of the cells' available glutathione, leaving enzymes glutathione-dependent unable to function. Several enzymes that are important in cellular respiration, the process by which large molecules are broken down and provide the cell with energy, are glutathione-dependent. Their inhibition leads to chlorothalonil's toxic effects.[5]

Figure 1
Chlorothalonil



2,4,5,6-tetrachloroisophthalonitrile

Acute Toxicity

Chlorothalonil's acute toxicity through ingestion is low; the median lethal dose (LD_{50}; the amount that kills half of a population of test animals) for laboratory animals is between 5 and 10 grams of chlorothalonil per kilogram of body weight.[6]

However, chlorothalonil's toxicity is much greater when exposure occurs through inhalation. The median lethal concentrations (LC_{50}s) of chlorothalonil or chlorothalonil-containing products are between 0.09 milligrams per liter (mg/l) of air and 0.54 mg/l. This places its inhalation toxicity in the highest two toxicity categories defined by the U.S. Environmental Protection Agency (EPA).[6]

Acute exposure to chlorothalonil also causes eye irritation. Tests summarized by EPA show that both chlorothalonil

Caroline Cox is JPR's editor.

and chlorothalonil-containing products cause rabbits' corneas to become opaque, as well as causing the white of the eyes to become irritated and develop ulcers. In some tests opaque corneas lasted up to 14 days after exposure, and chlorothalonil was corrosive to eyes in other tests.[6]

Acute effects of chlorothalonil have been shown at the cellular level. Incubation of rat liver cells with chlorothalonil caused oxidation of lipids (fatty substances) and decreased cell viability.[7]

Skin Irritation and Allergic Reactions

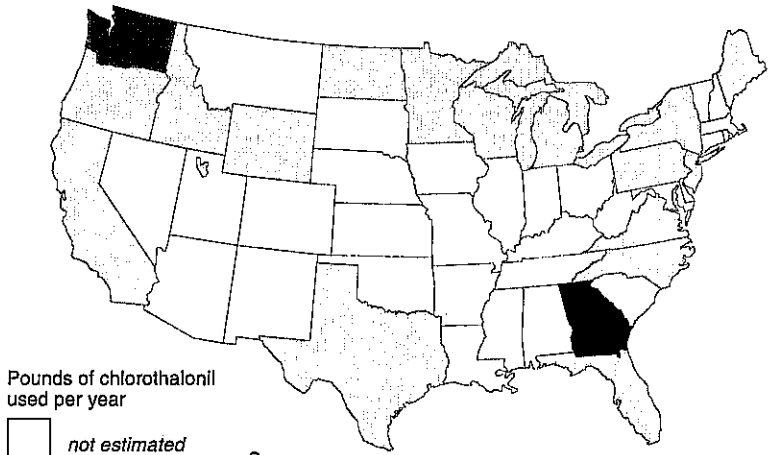
Chlorothalonil often causes skin rashes (dermatitis). When people are exposed repeatedly, their skin can become sensitized so that they develop allergic reactions to the fungicide. Greenhouse workers,[8,9] nursery workers,[8,9] field workers on banana plantations,[10] workers in chlorothalonil manufacturing plants,[11] painters,[12] and home gardeners have all developed skin rashes and sensitivities.

In some cases, the sensitization can be severe. For example, one nursery worker went to visit her physician because of a facial rash and swelling that developed regularly when she arrived at work. The physician, suspecting chlorothalonil allergy, gave her a standard skin allergy test. This small exposure sent the patient into shock and required immediate treatment.[8]

The reactions can also be persistent: a gardener who repeatedly used chlorothalonil developed a rash that persisted for a year after he stopped using chlorothalonil.[13]

Probably the most notorious case of chlorothalonil sensitivity involves Lieutenant George Prior, who died a month after playing golf in Arlington, Virginia in 1982. During that month he suffered from a mysterious illness that began with headache and fever, and ended with large blisters on his arms and back, kidney failure, aspiration pneumonia, and extreme pain. Navy pathologists concluded that the disease was caused by the chlorothalonil used on the golf course twice during the week prior to his game.[14]

Figure 2
Agricultural Uses of Chlorothalonil in the United States



Sources:

U.S. Dept. of Agriculture. National Agricultural Statistics Service. Economic Research Service. 1992. Agricultural chemical usage: 1991 field crops summary. Washington, D.C. (March.)
U.S. Dept. of Agriculture. National Agricultural Statistics Service. Economic Research Service. 1997. Agricultural chemical usage. Vegetables: 1996 summary. Washington, D.C. (July.)

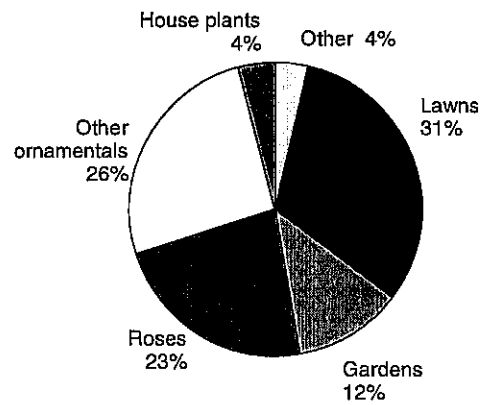
Chlorothalonil's major agricultural use is on peanuts in Georgia. In the Pacific Northwest, major uses are on potatoes and onions.

Subchronic Toxicity

Tests with laboratory animals have shown that consumption of a chlorothalonil-contaminated diet over a period of weeks or months has caused a variety of adverse health effects, mostly involving the kidney.

Rats: In rats fed chlorothalonil-contaminated food for 22 weeks, dilation of kidney tubules occurred at all doses tested. Similar results were found in rats fed chlorothalonil-contaminated food for 90 days. In a third study using lower doses of chlorothalonil, cell division in the lining of the kidney increased in males at the highest dose tested and

Figure 3
Household Uses of Chlorothalonil



Source: Whitmore, R.W., J.E. Kelly, and P.L. Reading. 1992. National home and garden pesticide use survey. Final report, Volume 1: Executive summary, results, and recommendations. Research Triangle Park NC: Research Triangle Institute. Prepared for U.S. EPA. Office of Pesticides and Toxic Substances. Biological and Economic Analysis Branch.

Lawns, roses, and other ornamental plants account for most of the household uses of chlorothalonil in the United States.

kidney weights were increased at the top two doses. This test also showed increased cell division in the lining of the forestomach, as well as an increase in the size of the cells.[15] A fourth study using both chlorothalonil and a derivative formed when chlorothalonil moves through the digestive system found that both compounds caused similar kidney effects.[16]

Mice: A thirteen-week study of mice showed that kidney weights increased at the top two doses tested. At the top three doses this study also showed effects on the forestomach similar to those found in rats: increased cell division and cell size in the lining of the stomach and ulceration of the mucous membrane.[17]

Chronic Toxicity

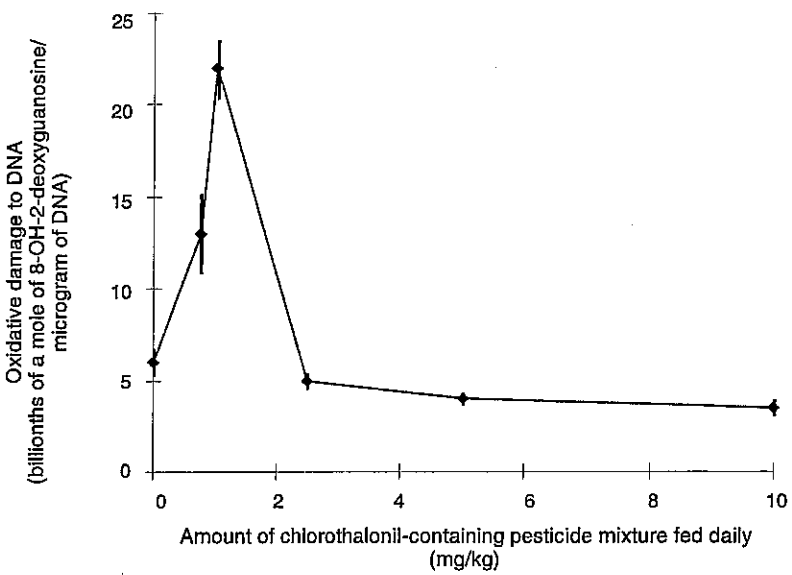
Long-term (chronic) studies of laboratory animals that have been fed chlorothalonil-contaminated food show effects that are similar to those found in subchronic studies. In addition, they also show a variety of effects on other organs.

Rats: A two-year feeding study found that increased kidney weights, kidney damage, and increased cell division in the kidney tubules occurred at all doses tested. In the forestomach and esophagus, increased cell division and cell enlargement also occurred at all doses. Inflammation of arteries and increased cell division in the parathyroid also occurred in treated animals. A second study used lower doses of chlorothalonil because the first study had found effects at all doses and found similar effects on the kidney and forestomach at all but the lowest dose tested.[18]

Mice: A two-year feeding study found that increased kidney weights, inflammation of part of the kidney, degeneration of the kidney tubules, and kidney cysts occurred at all doses tested. In addition increased cell division and cell enlargement in the forestomach occurred. As with rats, a second two-year study looked at lower doses. This study found similar effects on the kidney at all but the two lowest doses, and effects on the forestomach at all but the lowest dose.[19]

Dogs: A two-year study with beagles found that eating chlorothalonil-contaminated food caused mild anemia; an increase in thyroid, liver, and kidney weights; gastritis; and excessive growth of cells in the kidney tubules at all but the lowest dose tested. In the liver, development of fibrous tissue in the liver's portal vein and increased cell division and inflammation of the bile duct occurred at all doses tested. A second dog study at lower doses did not find these effects.[20]

Figure 4
Genetic Damage Caused by a Mixture of Chlorothalonil and Other Pesticides



Source: Lodovici, M. et al. 1994. Effect of a mixture of 15 commonly used pesticides on DNA levels of 8-hydroxy-2-deoxyguanosine and xenobiotic metabolizing enzymes in rat liver. *J. Environ. Pathol. Toxicol. Oncol.* 13(3):163-168.

Chlorothalonil in a mixture of other pesticides causes oxidative DNA damage at low levels of exposure, but not at high ones. Further testing showed that chlorothalonil alone caused the same type of DNA damage.

Effects on Reproduction

Chlorothalonil has caused reproductive problems in laboratory studies. When rats were administered chlorothalonil on days 6 through 15 of pregnancy, the highest dose tested caused an increase in the number of early embryos that failed and were absorbed into the mother's body and an increase in the number of embryos that were lost following implantation into the wall of the uterus. In a second study, the offspring of rats fed chlorothalonil over two generations weighed less than the offspring of unexposed rats.[21] A study of rabbits dosed with chlorothalonil on days 6 through 18 of pregnancy found that at the highest dose tested the number of implanted embryos and the number of live fetuses was reduced.[22]

Mutagenicity

Although chlorothalonil proponents refer to chlorothalonil as "not genotoxic,"[23] (toxic to genetic material) the fungicide has caused genetic damage in mammals in studies of both live animals and cell cultures.

A research project at the University of Florence measured pesticide residues in the typical diet of an adult resident of central Italy. The fifteen most commonly detected pesticides were fed to rats for ten days in the proportion that they were found in the diet. Then DNA (genetic material) from the livers of these rats was

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P.O. BOX 1393, EUGENE, OREGON 97440 / (541)344-5044

analyzed for oxidative damage. (The oxidative damage studied in this experiment "causes misreplication of DNA that may lead to mutations or cancer.") Oxidative damage increased dramatically at the two lowest doses tested, but not at higher doses.[24] (See Figure 4.) A follow-up study showed that of the 15 pesticides in the mixture used in the first study, only two caused DNA damage when administered alone: chlorothalonil and the post-harvest pesticide diphenylamine. The authors conclude that excluding the use of these pesticides on food for human consumption would reduce the risk of DNA damage from ingestion of food.[25]

Two studies of cell cultures have shown that chlorothalonil induces genetic damage: DNA damage occurred in cultures of human white blood cells when chlorothalonil exposures were at low concentrations and of short duration,[26] and mutations occurred in cultures of mouse lymphoma cells.[27]

These laboratory studies are consistent with the results of a study of pesticide-exposed greenhouse sprayers which found that exchanges of genetic material between sister chromosomes, "a sensitive indicator of genotoxicity," were increased in greenhouse workers exposed to chlorothalonil and other pesticides.[28]

Carcinogenicity

Chlorothalonil's ability to cause cancer has been relatively well studied and is a serious concern. EPA classifies chlorothalonil as a B2 (probable human) carcinogen.[29]

In two-year studies of two different strains of rats, increases occurred in kidney tumors and cancers as well as tumors and cancers of the forestomach. In mice, increases occurred in tumors and cancers of the forestomach in both sexes and increases in kidney tumors and cancers occurred in males.[21]

Chlorothalonil proponents have argued that EPA's carcinogenicity classification for chlorothalonil needs revision because the results of the rodent laboratory tests are not relevant to humans. They make the following three assertions: chlorothalonil is not genotoxic; forestomach cancers are not relevant to humans, who do not have a forestomach; and chlorothalonil's kidney tumors are caused by formation of thiol derivatives of chlorothalonil, a molecule that is formed about ten times more readily in rats than in humans.[23] All three of these arguments can be refuted. First, chlorothalonil can be genotoxic. (See "Mutagenicity," above.) Second, while forestomach cancers may not be relevant to humans, certainly the kidney cancers occur in an important human organ. Third, kidney cancers occur in mice, whose ability to form thiol derivatives of chlorothalonil is comparable to that in humans.[30]

Occupational Exposure

Farmworkers are exposed to chlorothalonil when they mix the pesticide, load application equipment, act as flaggers for aerial application, or do field work. Two estimates have been made of the hazards this exposure might pose to their health.[31,32] Both studies found that mixers and loaders can be exposed to amounts of chlorothalonil significantly above the levels EPA calculates as acceptable. The exposure of mixer-loaders is up to 1,000 times the average daily exposure considered by EPA not to cause adverse effects. The cancer risk to mixer-loaders is about 1,000 times the level EPA considers acceptable,[31,32] while the risk to flaggers and field workers is about 50 times the risk EPA considers acceptable.[32]

Contamination of Food

Residues of chlorothalonil are regularly found on produce that was grown using the herbicide. For example, the U.S. Dept. of Agriculture found chlorothalonil residues on 32 percent of their celery samples and 7 percent of their green bean samples in 1992;[33] 50 percent of the celery samples and 12 percent of the green bean samples in 1993;[34] and 14 percent of the green bean samples in 1995. (Celery was not sampled in 1995.)[35]

Contamination of Water

Chlorothalonil does not have the chemical properties of a molecule that is likely to leach through soil and contaminate water. However, it has been found in groundwater in four states: California, Florida, Massachusetts, and Maine. In addition, it binds strongly to organic acids in water which can result in elevated concentrations in water, like cranberry bogs, that contains these acids.[36]

Chlorothalonil's ability to contaminate water long distances from where it is used was startlingly demonstrated in a U.S. Dept. of Agriculture study of the Bering Sea. Chlorothalonil was found in every fog sample collected, and in several of the sea water samples collected.[37]

Contamination of Air

Air is often contaminated with chlorothalonil. For example, EPA found chlorothalonil in indoor air, outdoor air, and in personal air samplers carried by study participants in its Nonoccupational Pesticide Exposure Study. The study looked at residents of two towns, Springfield, Massachusetts, and Jacksonville, Florida, during 2 or 3 seasons. The study estimated that 20 percent of Jacksonville residents are exposed to chlorothalonil in winter indoor air and 12 percent of Springfield residents are exposed to chlorothalonil in spring outdoor air.[38]

Chlorothalonil is able to travel in the air a significant distance from an application site. A study in North Dakota found chlorothalonil in air sampled almost a mile from farmland where the fungicide was used.[39] California air monitoring found chlorothalonil not only at application sites, but also in nearby residential areas.[40]

Persistence in Soil

Chlorothalonil's half-life in soil (the length of time required for half of the quantity of chlorothalonil applied to break down or move away from the application site) is identified by both EPA and the World Health Organization as approximately 1 to 2 months.[41,42] Persistence (the length of time for residues to completely disappear) in soil is longer. NCAP located only two published stud-

ies (located in the same area) measuring the persistence of chlorothalonil. One indicated that chlorothalonil persisted at least one year, at which time chlorothalonil was reapplied so it was not possible to determine complete persistence.[43] The other measured a persistence of 200 days.[44]

Effects on Fish

Chlorothalonil is acutely toxic to fish: concentrations of less than 100 parts per billion (ppb) are typically fatal. For example, the median lethal concentration (LC_{50}) for rainbow trout varies between 10 and 76 ppb;[45] for channel catfish LC_{50}s between 52 and 90 ppb have been reported;[46] and an LC_{50} of 27 ppb has been measured for the stickleback.[45] Chlorothalonil is "very highly toxic" to all of these species by EPA criteria.

Sublethal effects of chlorothalonil exposure occur in fish at concentrations significantly lower than the LC_{50}. In rainbow trout, concentrations of 2 ppb reduced the diffusive capacity of the gills to about 40 percent of that of unexposed fish. The same concentration reduced hematocrit levels in the trout's blood to 65 percent of normal, resulting in "severe anemia."[47]

A test of the effects of exposure to sheepshead minnows during the entire life cycle showed that chlorothalonil concentrations of 6.5 ppb caused decreases in the number of eggs, the hatchability of the eggs, and the survival of fry.[45]

Chlorothalonil tends to concentrate in fish tissues (bioconcentrate) above the levels found in the water in which the fish are living. Measured bioconcentration factors vary from 16 in catfish to 940 in rainbow trout.[48]

Fish kills and respiratory distress in fish at trout farms have been reported after spraying of potato fields,[47] and fish kills have been reported after spraying of cranberry bogs[36] with chlorothalonil.

Effects on Other Aquatic Animals

By EPA criteria, chlorothalonil is "highly toxic" (with an LC_{50} between 100 and 1000 ppb) to Dungeness crab larvae, pink shrimp, frogs, and water fleas. As observed with fish, sublethal effects occur at much lower concentrations. For example, 7 ppb causes reduced shell growth in oysters, less than 100 ppb causes immobilization of dungeness crab larvae, and 2 ppb causes immobilization of water fleas.[45] Less than 40 ppb reduced activity of the neurotransmitter acetylcholinesterase in three species of freshwater crustaceans.[49]

Frog kills have been reported after chlorothalonil treatment of cranberry bogs.[36]

Effects on Biological Control Agents

Biological control, "the suppression of pest organisms by their natural enemies,"[50] has been called "the most acceptable long-range control tactic available for incorporation into pest management programs."[50] Unfortunately, the use of pesticides can disrupt the successful use of biological control agents and "disruptions such as these dominate contemporary agricultural production systems."[51]

Chlorothalonil is not an exception to these general observations. For example, chlorothalonil reduced the viability of spores of *Bacillus popillae*, the causal agent of milky disease which is used as a biological control for the Japanese beetle. Chlorothalonil also inhibited vegetative cell growth of the milky disease microorganism at concentrations less than those that recommended for use on turf.[52] The pest fly onion maggot has a complex of natural enemies, including the parasitoid wasp *Aphaereta pallipes* and the pathogenic fungus *Entomophthora muscae*. Both of these organisms are more susceptible to mortality from chlorothalonil than the onion maggot, so use of chlorothalonil disrupts biological control.[51]

Effects on Other Animals

Adverse effects of chlorothalonil have been demonstrated in three other types of animals:

• Earthworms reared in chlorothalonil-contaminated soil had a life-span about 50 percent less than those reared in untreated soil. In addition, reproduction was virtually eliminated. The amount of chlorothalonil added to the soil in this study was equivalent to 5 times the recommended application rate.[53]

• Earwigs exposed to chlorothalonil residues on peanut foliage suffered 10 to 20 percent mortality. Residues of chlorothalonil on their food (armyworms) caused between 25 and 55 percent earwig mortality.[54]

• Eating a chlorothalonil-contaminated diet caused reproductive impairment in bobwhite quail at the middle and high dose used in a feeding study. Effects included reduced survival of quail offspring. A study with mallard ducks measured a reduction in egg production and hatching success at the high dose.[55]

Effects on Soil Microorganisms

The microorganisms that are responsible for breaking down cellulose (the main constituent of plant tissues) in soil are strongly inhibited by chlorothalonil under dry, flooded, or transitional conditions. Concentrations of 150 ppb (the recommended application rate) "completely" inhibited the breakdown of cellulose, while inhibition was "strong" at 1/10 of that concentration.[56]

Effects on Plants

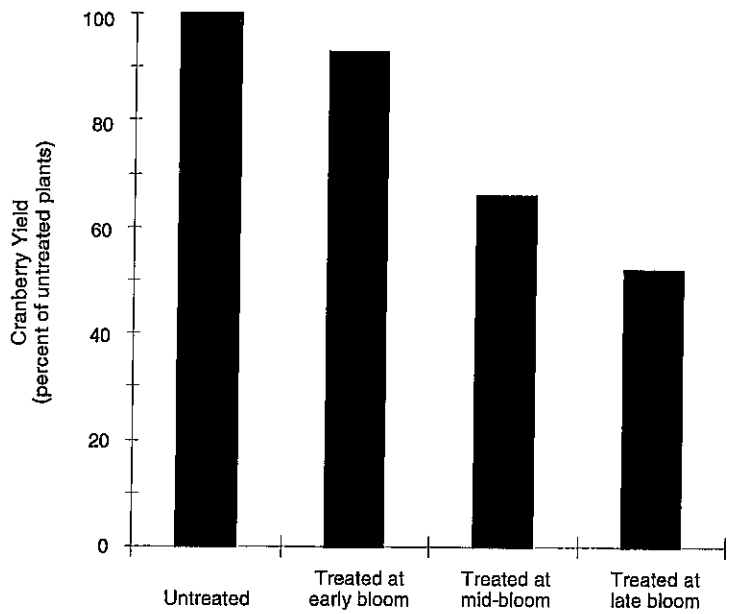
Although perhaps unexpected for a fungicide, chlorothalonil has a variety of effects on plants. These include direct mortality, growth inhibition, reductions in yield of crop plants, effects on mycorrhizal fungi, and other impacts.

• According to EPA criteria, chlorothalonil is "highly toxic" to the algae *Scenedesmus subspicatu*. The LC_{50} for this species is 515 ppb.[45]

• Chlorothalonil inhibited the survival, multiplication, and growth of shoots propagated from *Eucalyptus* trees. Some effects persisted after transplanting to fungicide-free soil.[57]

• Chlorothalonil treatment of Kentucky bluegrass increased the incidence of the disease stripe smut on one variety

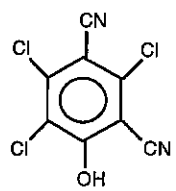
Figure 5
Reduction in Cranberry Yield Caused by Chlorothalonil Treatment



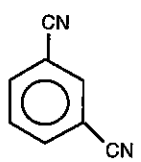
Source: Jeffers, S.N. 1991. Effects of fungicides applied during bloom on yield, yield components, and storage rots of cranberry. *Plant Dis.* 75:244-250.

Using chlorothalonil to control storage rot in cranberries requires treatment while the plant is still blooming. This can reduce cranberry yields up to 50 percent.

Figure 6
Chlorothalonil's Metabolites



4-hydroxy-2,5,6-trichloroisophthalonitrile



m-phthalodinitrile
(also known as isophthalonitrile)

of bluegrass and increased the incidence of the disease summer patch on three varieties.[58]

- Pollen germination in muskmelon is inhibited by chlorothalonil, possibly contributing to reduced fruit set.[59]
- Chlorothalonil treatment of cranberries to reduce post-harvest storage rot reduced cranberry yield significantly.[60] (See Figure 5.)
- Russeting (a condition where the skin becomes rough and brown and fruit growth ceases) of grapes is induced by chlorothalonil.[61]
- Chlorothalonil, in some regions of the country, has been "the chief phytotoxic offender" among fungicides used on ornamental roses.[62]
- The mutually beneficial interaction between mycorrhizal fungi and plants can be disrupted by chlorothalonil. (Mycorrhizal fungi are beneficial fungi that provide plants with improved uptake of water and nutrients.) In studies with the tropical tree *Leucaena leucocephala*, chlorothalonil at all concentrations tested reduced colonization of roots by mycorrhizae, uptake of the nutrient phosphorus, and dry matter yields.[63] Effects persisted for three months.[64]

Contaminants

Chlorothalonil is contaminated during its manufacture with hexachlorobenzene.[65] Hexachlorobenzene (which was itself used as a pesticide until all uses were cancelled in 1984) is classified by EPA as a probable human carcinogen, like chlorothalonil, because it causes liver, kidney, and thyroid tumors in rats, mice, and hamsters.[29] It also causes a wide spectrum of other adverse health effects: impaired immune system function, porphyria, kidney damage, effects on the thyroid, tremors, and reduced fertility. Hexachlorobenzene bioaccumulates in both animals and plants and is persistent, with a half-life in soils of between 3 and 6 years.[66]

Metabolites

The primary metabolite (breakdown product) of chlorothalonil is 4-hydroxy-2,5,6-trichloroisophthalonitrile. (See Figure 6.) It is found in soil, plants, and animals during the breakdown of chlorothalonil.[67] It about 30 times is more acutely toxic than chlorothalonil itself and is more persistent[68] and mobile in soil.[69] In subchronic toxicity tests, the 4-hydroxy metabolite caused a decrease in weight, anemia, and damage to bone marrow, spleen, liver and kidney. In chronic toxicity tests it caused anemia in rats and mortality and a buildup of fibrous proteins in the spleen.[70]

Another breakdown product formed in soil is m-phthalodinitrile. (See Figure 6.) While m-phthalodinitrile can cause headaches, nausea, confusion, and loss of consciousness,[71] in general its toxicological properties have not been investigated.[72]

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